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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/638,647	08/14/2000	David M. Stern	0575/62176/JPW/JML	9844

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EXAMINER	
CROUCH, DEBORAH	
ART UNIT	PAPER NUMBER
1632	7

DATE MAILED: 09/24/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/638,647	STERN ET AL.	
	Examin r	Art Unit	
	Deborah Crouch	1632	

-- The MAILING DATE of this communication app ars on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Claims 1-8 are pending.

The present specification objected to for the following reasons. Appropriate correction is required.

1. Multiple references to RAGE transgenic mice (see page 4, line 21, page 6, line 29, page 7, lines 1 and 10, page 14, lines 12-17, page 32, line 29, 33, line 1, page 39, line 15-16, and page 55, line 9.)

2. The present of reference numbers in the text, but the references listed do not correspond. (See pages 29, 32, 35, 39 and 70 as examples.)

3. Two sets of figure legends, of which only the first corresponds to the figures (pages 4-7 and pages 77-82). All figure legends should be at one place in the specification.

4. Two lists of references. There should be only one list at the end of the specification. (See pages 72-77 and pages 84-89.)

5. The legends for figures 4, 11, 12 and 13 each mentions "RAGE", but no "RAGE" is indicated on the figures.

6. There is no period at the end of the sentence at page 32, line 17.

Applicant should not take the examiner's examples of inconsistencies or improprieties as complete. Applicant should review the specification for all the above listed problems and any others.

The abstract of the disclosure is objected to because legal phraseology is contained therein. Correction is required. See MPEP § 608.01(b).

The attempt to incorporate subject matter into this application by reference to APP transgenic mice produced by Dr. Lennart Mucke is improper because 1) there is no "Mucke" listed as reference 14, and 2) if the reference is to a publication, this would be improper as reference can only be made to a published US patent or an allowed US application. The mice referred to as having been produced by Dr. Lennart Mucke are considered essential to the

invention, and as such must be from a reproducible source, readily available to the public. In this particular instance as there is no reference to a relevant publication, no material may be incorporated into the specification from a reference.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification discloses only that transgenic mice were generated by crossing mice comprising a nucleic acid construct comprising a DNA sequence encoding human ABAD operably linked to a PDGF promoter with transgenic mice comprising a nucleic acid construct comprising a DNA sequence encoding a mutant amyloid precursor protein hAPP695, hAPP751 and hAPP770. The doubly transgenic mice exhibit the phenotypes of claim 1 and 5. However, at the particular disclosure, there is no clear description of the transgene that was used in the production of transgenic mice comprising a nucleic acid construct comprising a DNA sequence encoding a mutant amyloid precursor protein hAPP695, hAPP751 and hAPP770 having familial AD mutations (specification, page 32, line 29 to page 33, line 3). Without a clear description of the particular transgene, that is DNA sequence, DNA construct, or promoter, used to make these mice, or other mice that could also be used in the production of PD-ABAD/hAPP mice, the specification at most only enables mice produced by across between PD-ABAD and hAPP. Note additional confusion at this point in the specification by reference to PD-RAGE mice. Furthermore, the only reference or guidance to

the hAPP mice is attributed to Dr. Lennart Mucke. A third party source is insufficient to provide a source for these mice as there is no guarantee that the mice will be readily available to the public. Since the hAPP mice are required to make the claimed mice and the mice of the methods claimed, these mice are seen as essential to the implementation of the invention. However, the lack of a source or a means to make the hAPP mice renders the production of PD-ABAD/hAPP mice non-enabled.

To overcome this lack of enablement, applicant can deposit PD-ABAD/hAPP mouse embryos. (37 CFR 1.802.) If the deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the specific mouse embryos has been deposited under the Budapest Treaty and that the strain will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein. 37 CFR 1.808

If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.808, applicants may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer;

(d) a viability statement in accordance with the provisions of 37 CFR 1,807; and

(e) the deposit will be replaced if it should ever become inviable.

As required under 37 CFR 1.809(d), the specification shall contain: (1) the accession number for the deposit; (2) the date of deposit; (3) a description of the deposited biological material sufficient to identify it and to permit its examination; and (4) the name and address of the depository.

Once the deposit of PD-ABAD/hAPP embryos has been made or assured, applicant will be limited to a transgenic mouse of strain PD-ABAD/hAPP and methods for evaluating in PD-ABAD/hAPP mouse, does not reasonably provide enablement for a transgenic nonhuman animal and methods of evaluating using the transgenic nonhuman animal. The mouse of the claims possess a detailed phenotype of reduced basal synaptic transmission, inhibited synaptic plasticity, increased neuronal stress, elevated 4-hydroxynoneal in cerebral cortex, increased heme oxygenase type I in cerebral cortex, decreased synaptophysin in cerebral cortex, decreased microtubule-associated protein-2 in cerebral cortex, or increased levels of activated caspase 3 antigen in cortical neurons. This is unpredictable because the art at the time of filing taught that the production of transgenic mice expressing an APP transgene sufficiently to produce a useful phenotype is unpredictable.

At the time of filing, the transgenic art taught that expression of a transgene was unpredictable because of poor expression of the transgene due to the insertion site of the transgene into the genome. Well-regulated transgenic expression is not frequently achieved because of poor levels or the complete absence of expression or leaky expression in non-target tissues (Cameron (1997) Molec. Biol. 7, page 256, col. 1 -2, bridg. parag.). Factors influencing low expression, or the lack their of, are not affected by copy number and such effects are seen in lines of transgenic mice made with the same construct (Cameron (1997),

Molec. Biol. 7, page 256, lines 3-9). These factors, thus, are copy number independent and integration site dependent, emphasizing the role the integration site plays on expression of the transgene (Cameron (1997), Molec. Biol. 7, page 256, lines 10-13). Further, Sigmund (2000) states that the random nature of transgene insertion, resulting founder mice can contain the transgene at a different chromosomal site, and that the position of the transgene effects expression, and thus the observed phenotype (Sigmund (2000) Arteroscler. Throm. Vasc. Biol. 20, page 1426, col. 1, parag. 1, lines 1-7). With regard to the importance of promoter selection, Niemann (1997) states that transgenic pigs made with different promoters regulating expression of a growth hormone gene give disparate phenotypes - one deleterious to the pig, the other compatible with pig health (Niemann (1997) Transg. Res. 7, page 73, col. 2, parag. 2, line 12 to page 73, col. 1, line 4). In addition, the art also taught that the production of transgenic mice expressing an APP transgene had been problematic, and that the reason was mice as a species may be resistant to the formation of Alzheimer's related pathologies and that sufficient expression of the APP transgene may be difficult to achieve (Lannfelt et al (1993) Behav. Brain Res. 57. page 210, col. 1, parag. 5; and col. 2, parag. 4, lines 8-16). In fact, transgenic mice, which express the human APP-695 gene, were known in the art not to form amyloid protein deposits or neuritic processes (Higgins et al (1993) Annals NY Acad. Sci. 695, abstract). Also, at the time filing, the art taught that transgenic rats containing an APP transgene failed to demonstrate any Alzheimer's related pathology at six months of age (Felsenstein et al (1995) Alzheimer's and Parkinson's Diseases, I. Hanin, ed., Plenum Press, New York, page 406, page 1). Thus the production of any transgenic animal model of Alzheimer's Disease with the particularly claimed phenotypes would have been regarded as unpredictable due to the above discussed art recognized problems with transgenesis in general.

Further, the claims require that the DNA sequence encoding hAPP695, hAPP751 and hAPP770 each having familial AD mutations. The only parental mouse disclosed by the specification is the one attributed to Dr. Lennart Mucke, the hAPP mouse. As discussed above, this mouse is not sufficient described as how it was made that the skilled artisan would be able to reproduce it or others like it.

Therefore, for the reasons discussed above, the skilled artisan at the time of the instant invention would have needed to engage in an undue amount of experimentation without a predictable degree of success to implement the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 5 state in part (b) that the mouse contains "... a DNA sequence encoding a mutant human amyloid precursor protein HAPP695, hAPP751 and hAPP770 ..." This phrase is confusing as each APP listed is a splice variant of APP. It is not clear if applicant means the DNA sequence gives rise to all three splice variants in the doubly transgenic mice.

Claims 1 and 5 state ABAD is amyloid-beta peptide alcohol dehydrogenase. The art defines an ABAD as amyloid-beta peptide binding alcohol dehydrogenase and as amyloid beta binding alcohol dehydrogenase. Are these the same dehydrogenases. Because the names and function appear to be similar, it is confusing as to the relation of the enzymes.

The claims are free of the prior art. The prior art did not teach or suggest transgenic nonhuman animals whose cells contain a DNA sequence comprising a nerve tissue specific promoter operatively linked to a DNA sequence which encodes amyloid-beta peptide alcohol dehydrogenate and a DNA sequence comprising a nerve tissue specific promoter operatively linked to a DNA sequence encoding a mutant human amyloid precursor protein hAPP695, hAPP751 and hAPP770 bearing mutations linked to familial Alzheimer's Disease in human, wherein said nonhuman animal exhibits at least one phenotype from the group consisting of: reduced basal synaptic transmission, inhibited synaptic plasticity, increased neuronal stress, elevated 4-hydroxynoneal in cerebral cortex, increased heme oxygenase type I in cerebral cortex, decreased synaptophysin in cerebral cortex, decreased microtubule-associated protein-2 in cerebral cortex, and increased levels of activated caspase 3 antigen in cortical neurons, or methods of using these mice in methods for evaluating the potential therapeutic effect of an agent for treating Alzheimer's Disease.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 703-308-1126. The examiner can normally be reached on Mon.-Thur., 8:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Deborah Crouch

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

dc
September 13, 2002